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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,040	11/15/2000	Paul J. Carter	P0710P1D1	5212

7590 08/28/2002
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Genentech Inc
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South San Francisco, CA 94080-4990

EXAMINER

YU, MISOOK

ART UNIT	PAPER NUMBER
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1642

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DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n N .

09/714,040

Applicant(s)

CARTER, PAUL J.

Examiner

Misook Yu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25, 28 and 29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25, 28 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) Z.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of I in Paper No. 9 is acknowledged.

Claims 25, 28, and 29 are pending and examined on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 recites "entirely free of" but it is not clear what the metes and bounds are for the phrase. Is there any difference between *entirely free of* and *free of*?

Claim 25 recites "entirely homogenous" but it is not clear what the metes and bounds are for the phrase. What is the difference between homogenous and "entirely homogenous"?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make** the invention. The claims are drawn to a composition comprising monospecific $F(ab')_2$, wherein the monospecific $F(ab')_2$ is free of arsenite and free of intrachain disulfide bond at the hinge region, and homogenous at the heavy chain C-terminal end, wherein claim 28 further limits only one hinge region cysteine, wherein claim 29 specifies the C-terminal end to be Cys-Ala-Ala. The specification at Figures 1 and 2, page 9 and 10, page 28 to 32 teaches that monovalent Fab' fragment is obtained from expression of

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the protein in *E. coli* using recombinant DNA technology. The specification at page 8 lines 31-34 teaches that the monovalent purified protein is cross-linked using sulfhydryl chemical crosslinkers, DTNB or a bifunctional maleimide to produce $F(ab')_2$.

However, neither the specification nor the art teaches how to get homogenous protein molecules, $(Fab')_2$ as to the heavy chain C-terminal amino acid residues, especially when the protein is subjected to many proteolysis-inducing manipulations such as protein purification procedures and other chemical procedures. Although Pluckthun et al (1989, *Methods in Enzymology* vol. 178, pages 497-515) as well as the instant specification teach that expression of recombinant Fab' molecule in *E. coli* and manipulation of genetic code for producing a desirable amino acids in a protein is routine procedure at the effective filing date of the instant application, and Sambrook et al (1989, *IDS, Molecular Cloning: A Laboratory Manual*, 2nd Edition, pages 17.31-17.33) teach that the promoter and the vector used in the cloning of the Fab' fragment of the instant application was well known and used, Voet et al at page 77 (*Biochemistry*, 1990, John Wiley and Sons, Inc.) teach obtaining homogenous protein molecule is not plausible. The claimed monospecific $F(ab')_2$ has been subjected to proteolysis during expression, purification, chemical cross-linking procedure, and re-purification processes. Note the specification that cross-linking is performed at room temperature. Further, the specification does not disclose how to protect the last amino acid of the heavy chain from such attack. Nor it discloses how to distinguish the monospecific $F(ab')_2$ from a molecule $F(ab')_2$ that does not have last amino acid the monospecific $F(ab')_2$ because the last amino acid is lost due to proteolysis.

Glennie et al (1987, *J. Immunology* Vol. 139, pages 2367-2375) at page 2368 left column, 3rd paragraph, Figure 8 teach that it is possible to make $F(ab')_2$ molecules free of hinge region intradisulfide bond by cross-linking rabbit Fab' fragment which has only one SH group at the hinge region using o-PDM (one of the cross-linking agent used in the instant specification, note page 8 line 32) without introducing arsenite in the cross-linking reaction mixture. However, neither specification nor the art teaches how to cross-link two Fab' fragment with multiple SH groups at the hinge region without preventing formation of intrachain disulfide bond at the hinge region. US PAT.

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5,274,119 (Frazier et al., Dec. 28, 1993) teaches at column 16 and 17 that hinge region Fab-SH can easily form intradisulfide bond. Note also the first page figure of the US PAT. 5,274,119. A few molecules of any of Fab'-TNB, maleimidated Fab', or Fab'-SH might have formed hinge region intradisulfide bond. One skilled in art would not accept that 100 % of the molecules were prevented to have the hinge region intrasulfide bond formation in light of US PAT. 5,274,119 teachings. The specification does not teach how to get rid of the molecules with hinge region intrachain disulfide.

The one skilled would not accept without doubt it is possible to obtain homogenous F(ab')₂ as to the heavy chain C-terminal amino acid and free of having hinge region intrachain disulfide bonds in light of the facts that protein is susceptible to proteolysis, chemical reaction produces side reactions, and the hinge region disulfide bond at Fab' is formed easily.

Considering limited teachings and no working examples in the specification, unpredictability in art, it is concluded that undue experimentation is necessary to practice the invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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Misook Yu

August 23, 2002



MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800

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